Original Article

Kurume Medical Journal, 69, 227-235, 2022

The Evaluation of Gastric Emptying Using the ^{13}C-Acetate Breath Test in Neurologically Impaired Patients – A Focus on the Stomach Function and Morphology –

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Received 2 September 2022, accepted 20 December 2022
J-STAGE advance publication 16 February 2023

Edited by YOSHITO AKAGI

Summary: ***Purpose*:** We explored factors affecting gastric emptying in neurologically impaired (NI) patients using the ^{13}C-acetate breath test.
***Methods*:** Twenty-four NI patients were classified by the presence of gastroesophageal reflux disease (GERD), which was treated by fundoplication plus gastrostomy, or the absence of GERD, which was treated by gastrostomy alone, along with gastric malposition involving cascade stomach and organoaxial gastric volvulus (OGV). Gastric emptying parameters (GEPs), which were the emptying half time ($T_{1/2}$, minute), the lag phase time (T_{lag}, minute), and the gastric emptying coefficient (GEC), were measured before and after surgery. We evaluated the relationship between GEPs and GERD, gastric malposition, and surgical intervention. All data were expressed as the median (interquartile range).
***Results*:** The $T_{1/2}$ and GEC of patients with OGV were significantly worse than in those without OGV before surgery ($T_{1/2}$ with OGV: 241.3 [154.9, 314.3] vs. $T_{1/2}$ without OGV: 113.7 [105.2, 151.4], $p = 0.01$, GEC with OGV: 3.19 [2.46, 3.28] vs. GEC without OGV: 3.65 [3.24, 3.90], $p = 0.02$). GERD and cascade stomach were not associated with GEPs. The GEPs of all NI patients showed no significant difference between before and after surgery. The surgical change in $T_{1/2}$ ($\Delta T_{1/2}$) in the patients with OGV was significantly lower than in those without OGV ($\Delta T_{1/2}$ with OGV: −47.1 [−142.7, −22.1] vs. $\Delta T_{1/2}$ without OGV: −3.78 [−26.6, 12.0], $p = 0.03$).
***Conclusion*:** Stomach malposition, such as OGV, seems to affect gastric emptying and may be improved by surgical intervention.

Keywords ^{13}C-acetate breath test, fundoplication, gastric emptying, gastrostomy, neurological impairment, organoaxial gastric volvulus

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Abbreviations: ^{13}C-ABT, ^{13}C-acetate breath test analyses; DGE, delayed gastric emptying; GEPs, gastric emptying parameters; GERD, gastroesophageal reflux disease; LAG, laparoscopic assisted gastrostomy; NI, neurological impairment; OGV, organoaxial gastric volvulus; pH/MII, multichannel intraluminal impedance pH measurements; PEG, percutaneous endoscopic gastrostomy.

INTRODUCTION

Neurologically impaired (NI) patients often require tube feeding. Some of them require a nasogastric tube for enteral nutrition and pharmacotherapy. Trans-nasal feeding tube placement is a simple and effective procedure. However, it has several disadvantages, including constant irritation to the throat, the risk of accidental dislodgement, and occasional difficulty during insertion. Furthermore, long-term intubation with a nasogastric tube increases the risk of esophagitis, respiratory disorders, and gastroesophageal reflux disease (GERD). Therefore, many NI patients require surgical intervention to maintain a safe route for nutrition.

At present, percutaneous endoscopic gastrostomy (PEG) is the standard gastrostomy technique. However, NI patients usually undergo a permanent gastrostomy or fundoplication using the laparoscopic assisted gastrostomy (LAG) procedure because of anatomical difficulties of NI patients [1-4]. Additionally, several studies have shown that delayed gastric emptying (DGE), which is a medical disorder involving weak muscular contractions of the stomach, is common in NI patients with an incidence rate of > 50.0% [5-8]. Multiple factors such as gastro-intestinal motility, the autonomic nervous system, and gastric malposition may be associated with the pathophysiology of DGE [9]. In NI patients, gastric malposition such as chronic cascade stomach, which is defined as retroflexion of the fundus, and organoaxial gastric volvulus (OGV), which is defined as rotation of the stomach around the short-axis, are frequent body anomalies. To our knowledge, there are few reports about the effect of gastrostomy on gastric emptying (GE) focused on GERD and the stomach morphology in NI patients [10]. Since many NI patients were accompanied to DGE, it was crucial to know the factors affecting GE before and after surgery, such as LAG with fundoplication or not.

The present study clarified the factors affecting GE in NI patients using the noninvasive ^{13}C-acetate breath test (^{13}C-ABT), focusing on GERD and stomach morphology.

MATERIALS AND METHODS

This was a single-institution, retrospective study. All patients treated at Kurume University Hospital from July 2006 to December 2020 were included. This study was conducted after obtaining satisfactory informed consent from their patients' parents or caregivers. The study was approved by the ethics committee for clinical research of Kurume University School of Medicine (approval No. 11049).

Patients

A total of 24 NI patients (male, n=13 male; female, n=11) were included during the study period and were followed for >4 months after surgery. Before surgery, all patients had profound NI due to a congenital disorder (cerebral palsy [n = 10], chromosomal anomaly [n = 4]), or an acquired disorder (epilepsy [n = 5], hypoxic brain damage [n = 3], sequelae of cerebral hemorrhage [n = 1], or sequelae of meningitis [n = 1]) (Table 1).

Twenty-four-hour multichannel intraluminal impedance pH measurements

All patients underwent 24-h multichannel intraluminal impedance pH measurements (pH/MII). In the

TABLE 1.
Patient characteristics and gastric emptying parameters

Age (y)	13.5 (7.3, 18.8)
Body weight(kg)	21.0 (13.6, 28.5)
Body Height (m)	1.32 (1.02, 1.44)
BMI (kg/m^2)	13.3 (12.3, 14.5)
Gender (Male)	13 (54.2%)
Causative disease	
cerebral palsy	10 (41.7%)
chromosomal anomaly	4 (16.7%)
epilepsy	5 (20.8%)
hypoxic brain damage	3 (12.5%)
sequelae of cerebral hemorrhage	1 (4.2%)
sequelae of meningitis	1 (4.2%)
Preoperative findings	
GERD	
(+)	10 (41.7%)
(−)	14 (58.3%)
Cascade stomach	
(+)	8 (33.3%)
(−)	16 (66.7%)
Organoaxial gastric volvulus	
(+)	5 (20.8%)
(−)	19 (79.2%)

BMI; body mass index, GERD; gastroesophageal reflux disease. Data is expressed as median (25th , 75th interquartile range) or number (%)

analysis of pH/MII, a multiple intraluminal impedance catheter (outer diameter, 2 mm) with 2 pH antimony electrodes and 7 impedance electrodes (Sandhill Scientific, Inc., Highlands Ranch, CO, USA) was used. The catheter was inserted transnasally through the oesophagus. The 2 pH antimony electrodes were placed in the lower oesophagus and cardia of the stomach; each and position was confirmed by radiography. The data obtained from 24-hour pH/MII was automatically evaluated using the BioVIEW analysis software program (Sandhill Scientific, Inc., Highlands Ranch, CO, USA); each tracing was manually reviewed by the same investigators (D.M. and S.F.). Liquid reflux, defined by pH/MII as a $\geq 50\%$ decrease in impedance from the baseline, occurred in at least two consecutive channels in an aboral direction. Each type of reflux was defined as follows: acidic reflux was diagnosed in cases associated with a pH drop to ≤ 4, and non-acid reflux was diagnosed in cases associated with a nadir pH value > 4. The pH index was defined as the percentage of time that the pH was ≤ 4.0. We defined 4.0% as the upper cut-off value for GERD in accordance with the definition outlined in the NICE guidance 2015 [11]. The bolus exposure index was defined as the percentage of time with retrograde movement of intraluminal esophageal material. We defined 1.4% as the upper cut-off value. Pathological GERD was defined as a case in which the percentage of time that the pH exceeded 4.0% or the bolus exposure index exceeded 1.4%. GERD in all patients was evaluated and diagnosed in accordance with the above pH/MII parameters. If the patient was diagnosed with GERD based on the parameters of pH/MII, Nissen's fundoplication and LAG were also performed.

Upper gastrointestinal contrast study

For the diagnosis of gastric malposition, all patients underwent an upper gastrointestinal contrast study with gastrografin before and after surgery. Cascade stomach was defined as being present if fluid was observed pooling in the fundus (Fig. 1a). OGV was defined as an abnormal rotation of the stomach of more than 180° organoaxially (Fig. 1c). Upper gastrointestinal tract roentgenograms depicted the stomach morphology after surgery (Fig. 1b and 1d).

Surgical procedure

Patients without GERD underwent LAG only, while patients with GERD underwent fundoplication and LAG. LAG was performed under general anesthesia through a lower umbilical skin incision, and a 5-mm trocar was safely inserted into the abdomen using the OptiView procedure. Pneumoperitoneum was established with CO_2 insufflation. The stomach was identified using a 5-mm, 30° laparoscope. Under visual control with the laparoscope, a 5-mm trocar was inserted into the abdominal cavity at the right flank region. Through this port, the anterior stomach wall on the opposite side of the gastric angle was grasped with an instrument and elevated to the abdominal wall to determine the gastrostoma site. A 12-mm trocar was inserted at this point through the rectus muscle and into the abdominal cavity under visual control with a laparoscope. Through this port, the gastrostoma point of the stomach wall was grasped with clear margins from the pylorus and exteriorized when the grasper and trocar were pulled back. The stomach was then sutured to the rectus muscle fascia at four points, and a purse-string suture was performed around the stoma opening on the stomach wall. The gastrostomy tube was then inserted into the cavity of the stomach through a small incision in the stomach wall.

Nissen's fundoplication was performed as follows: three 5-mm trocars were inserted at the lower umbilicus as well as the right and left flank regions. A 12-mm trocar was inserted at the left flank region and a liver retractor was inserted at the epigastric region. The top part of the stomach was folded and sewn around the lower esophageal sphincter, a muscular valve at the bottom of the esophagus. If a hiatal hernia was diagnosed, it could be repaired at the same time. The hiatus opening in the diaphragm through which the esophagus passes was tightened. After completion of fundoplication and identification of the gastrostomy site on the gastric body, a gastrostomy was created with the same procedure mentioned above.

Evaluation of GE

For the evaluation of GE, the ^{13}C-acetate breath test analyses (^{13}C-ABT) (the Breath ID® system; Oridion Breath ID Ltd., Jerusalem, Israel) were used. ^{13}C-ABT was performed by accumulating the exhaled gas of the patients via the nasal cannula or tracheostomy cannula for breath testing. After more than 6 hours of fasting, all patients were given a calculated baseline breath test and administered 100 mL of the test meal, in which 100 mg of ^{13}C-labeled sodium acetate was dissolved. As a test meal, a semi-digested liquid meal (Racol®; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) was used. The nutrient compositions of 100 mL of Racol® were 4.4 g of protein extracted from casein and soybean, 15.6 g of carbohydrate, and 2.2 g of fat. The osmotic pressure of the meal was 330–360 mOsm/L. Before LAG, the test meal was administered

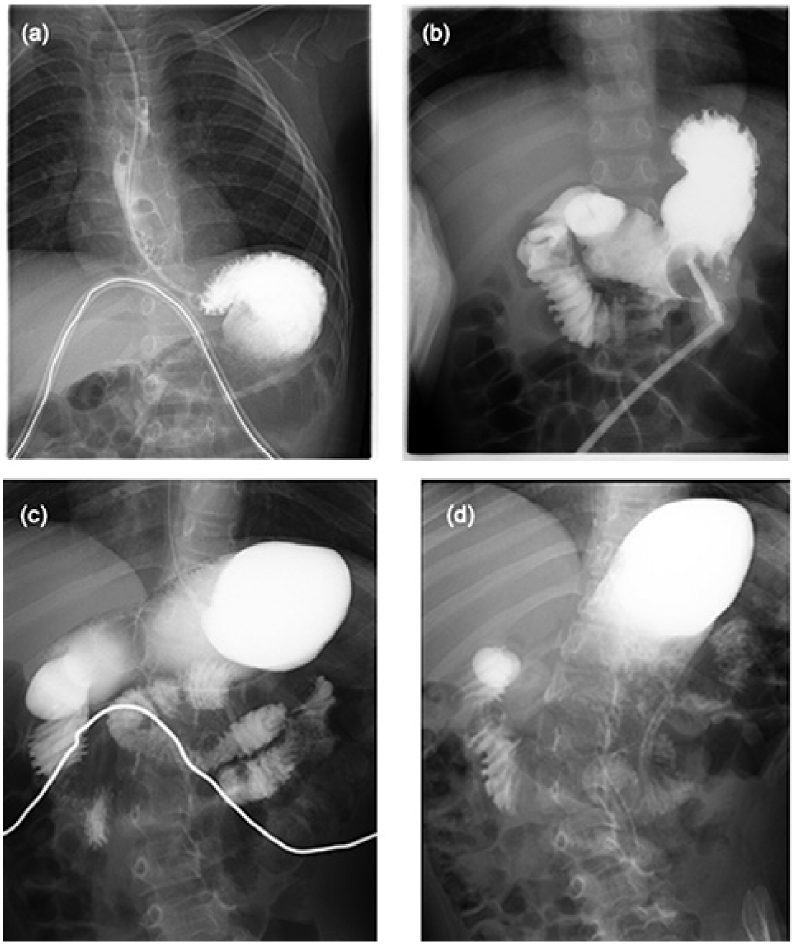

Fig. 1. Upper gastrointestinal study with gastrografin (a) Cascade stomach before laparoscopic assisted gastrostomy, (b) Cascade stomach after laparoscopic assisted gastrostomy, (c) Organoaxial gastric volvulus before laparoscopic assisted gastrostomy, (d) Organoaxial gastric volvulus after laparoscopic assisted gastrostomy.

within 5 minutes via a nasogastric tube. After LAG, the test meal was administered within 5 minutes via a gastrostomy tube. All patients were tested in the semi-Fowler's position. After absorption and metabolism of ^{13}C-labeled sodium acetate, ^{13}C was derived and exhaled as $^{13}CO_2$. The device continuously measures the ratio of ^{13}C and ^{12}C in the CO_2 of the exhaled breath using molecular correlation spectroscopy. The Breath ID® device measures the ratio and dose of ^{13}C substrate and provides the percentage dose recovery and cumulative percentage dose recovery as described in previous reports by Ishii et al. and Goose et al. [5,12]. It then calculates the half emptying time ($T_{1/2}$, minute) which is the time required for half of the gastric contents to be emptied, the lag phase time (T_{lag}, minute) which is the time at the point of inflection of the curve after mathematical integration, and the GE coefficient (GEC), which is an index of the global GE rate [5-7,13,14]. A shorter $T_{1/2}$ and T_{lag} and a higher GEC suggest accelerated GE. GE was expressed as $T_{1/2}$, T_{lag} and GEC were also evaluated as automatically analyzed GEPs. The data obtained from the ^{13}C-ABT were reviewed by the same investigator (S.I.).

Study design

The participants were prospectively followed, and patient characteristics were collected both before and after surgery, retrospectively. Patient characteristic data were as follows: evaluated age and BMI before and after LAG, presence or absence of GERD, cascade stomach and organoaxial gastric volvulus as gastric malposition, duration of days between ^{13}C-ABT before and after surgery, and GEPs about $T_{1/2}$, T_{lag} and GEC. $T_{1/2}$, T_{lag} and GEC before surgery were expressed as pre$T_{1/2}$, preT_{lag}, and preGEC, respectively; the corresponding values after surgery were expressed as post$T_{1/2}$, postT_{lag}, and postGEC, respectively. The change in GEPs before and after surgery were calculated as follows: $\Delta T_{1/2}$ = post$T_{1/2}$ – pre$T_{1/2}$, ΔT_{lag} = postT_{lag} – preT_{lag}, ΔGED= postGEC – preGEC.

First, patients were classified into groups according to the presence of GERD, cascade stomach, and OGV. Prior to surgery, the GEPs were evaluated and compared across groups. Additionally, the GEPs before and after surgery were compared between patients treated with LAG and fundoplication versus LAG only, as well as with and without cascade stomach and with and without OGV. Finally, changes in post-surgery GEPs were compared based on surgical procedures and the presence of cascade stomach or OGV.

Statistical analyses

All data were expressed as the median (interquartile range). All statistical analyses were performed using the JMP Pro 14 software package (SAS, Cary, NC, USA), and p values of < 0.05 were considered statistically significant. Comparisons of the patients before and after surgery were conducted using the chi-squared test and the Mann–Whitney U test. Variables were included when the p-value was < 0.05. P-values of < 0.05 were considered statistically significant.

RESULTS

Patient characteristics before surgery are detailed in Table 1. Ten patients were diagnosed with GERD and underwent LAG with Nissen's fundoplication; 14 patients were not diagnosed with GERD and underwent LAG only. Three patients underwent additional laryngotracheal separation, and 1 patient underwent additional laparoscopic cholecystectomy. An upper gastrointestinal study of gastric malposition revealed that 8 patients (33.3%) had cascade stomach and 5 patients (20.8%) had OGV (Table 1).

The comparison of preoperative GEPs in patients with and without GERD and the stomach morphology are detailed in Table 2. There were no significant differences in any of the GEPs between patients with GERD and those without, or between those with and without cascade stomach. Pre$T_{1/2}$ in patients with OGV was significantly longer, and preGEC was significantly lower in comparison to those without OGV [pre$T_{1/2}$ with OGV; 241.3 (154.9, 314.3) vs. pre$T_{1/2}$ without OGV: 113.7(105.2, 151.4), $p = 0.01$, preGEC with OGV; 3.19 (2.46, 3.28) vs. preGEC without OGV: 3.65 (3.24, 3.90), $p = 0.02$]. PreT_{lag} in patients with OGV was not significantly different from that in patients without OGV.

The comparison of GEPs before and after surgery, both with and without GERD, as well as with and without cascade stomach, and with and without OGV, is detailed in Table 3 and Fig. 2-4. There were no significant differences in GEPs.

The comparison of the change in GEPs between before and after surgery in patients who performed LAG with and without fundoplication and according to the stomach morphology is detailed in Table 4. GEP changes did not differ significantly between patients treated with LAGs with and without fundoplication or with and without cascade stomach. Only $\Delta T_{1/2}$ of pa-

TABLE 2.
Comparison of the preoperative gastric emptying parameters between the patient with and without GERD and morphology of the stomach (n=24)

	GERD (+) (n=10)	GERD (−) (n=14)	*p*
T_{lag} (min)	61.9 (51.6, 69.5)	66.0 (52.4, 110.8)	0.4642
$T_{1/2}$ (min)	123.8 (109.6, 154.8)	124.4 (102.1, 249.0)	0.8836
GEC	3.39 (3.30, 3.74)	3.45 (3.03, 3.96)	1.0000
	cascade stomach (+) (n= 8)	cascade stomach (−) (n= 16)	*p*
T_{lag} (min)	84.6 (49.3, 114.7)	62.8 (54.2, 67.9)	0.3123
$T_{1/2}$ (min)	144.1 (105.9, 251.9)	117.5 (109.1, 152.9)	0.5607
GEC	3.29 (2.83, 3.92)	3.52 (3.21, 3.9)	0.6238
	OGV (+) (n=5)	OGV (−) (n=19)	*p*
T_{lag} (min)	84.6 (50.2, 123.2)	65.0 (53.0, 68.4)	0.3555
$T_{1/2}$ (min)	241.3 (154.9, 314.3)	113.7 (105.2, 151.4)	0.0105
GEC	3.19 (2.46, 3.28)	3.65 (3.24, 3.90)	0.0207

GERD; gastroesophageal reflux disease, GEC; gastric emptying coefficient, OGV; organoaxial gastric volvulus.
Data is expressed as median (25th, 75th interquartile range)

TABLE 3.
Comparison of the gastric emptying parameters between before and after surgery (n=24)

	gastrostomy with funduplication (n=10)		*p*	gastrostomy (n=14)		*p*
	Before surgery	After surgery		Before surgery	After surgery	
T_{lag} (min)	61.9 (51.6, 69.5)	57.2 (47.0, 73.6)	0.4922	66.0 (52.4, 110.8)	66.4 (47.1, 89.8)	0.4548
$T_{1/2}$ (min)	123.8 (109.6, 154.8)	124.2 (107.2, 149.9)	0.9219	124.4 (102.1, 249.0)	133.3 (82.5, 172.1)	0.1726
GEC	3.39 (3.30, 3.74)	3.59 (3.26, 3.84)	0.7695	3.45 (3.03, 3.96)	3.48 (2.99, 3.79)	0.6698
	cascade stomach (+) (n= 8)			cascade stomach (−) (n= 16)		
	Before surgery	After surgery		Before surgery	After surgery	
T_{lag} (min)	84.6 (49.3, 114.7)	62.3 (43.6, 95.2)	0.25	62.8 (54.2, 67.9)	61.3 (49.5, 79.4)	0.5614
$T_{1/2}$ (min)	144.1 (105.9, 251.9)	132.6 (81.9, 205.2)	0.1484	117.5 (109.1, 152.9)	124.5 (104.1, 164.1)	0.7057
GEC	3.29 (2.83, 3.92)	3.61 (2.64, 3.83)	0.9453	3.52 (3.21, 3.9)	3.50 (3.18, 3.76)	0.9618
	OGV (+) (n=5)			OGV (−) (n=19)		
	Before surgery	After surgery		Before surgery	After surgery	
T_{lag} (min)	84.6 (50.2, 123.2)	83.2 (70.2, 92.4)	0.875	65.0 (53.0, 68.4)	52.6 (41.8, 72.1)	0.1671
$T_{1/2}$ (min)	241.3 (154.9, 314.3)	147.1 (132.5, 195.5)	0.125	113.7 (105.2, 151.4)	121.1 (89.4, 160.5)	0.5648
GEC	3.19 (2.46, 3.28)	2.81 (2.43, 3.67)	1.000	3.65 (3.24, 3.90)	3.60 (3.20, 3.83)	0.6722

GERD=gastroesophageal reflux disease, GEC=gastric emptying coefficient, OGV=organoaxial gastric volvulus.
Data is expressed as median (25th, 75th interquartile range)

tients with OGV showed significantly shorter in comparison to patients without OGV [$\Delta T_{1/2}$ with OGV; −47.1 (−142.7, −22.1) vs. $\Delta T_{1/2}$ without OGV; −3.78 (−26.6, 12.0), p=0.0291]. There were no significant differences in ΔT_{lag} and ΔGEC with and without OGV.

DISCUSSION

To our knowledge, the present study is the first clinical investigation to clarify the factors affecting GE in NI patients with a focus on GERD and the stomach morphology using the ^{13}C-ABT.

The major findings of this study were as follows: (1) the $T_{1/2}$ and GEC in patients with OGV were significantly longer than in patients without OGV before surgery, (2) there were no significant differences in the GEPs before and after surgery, (3) there were no significant differences in the change in GEPs between LAG with and without fundoplication, and (4) the change in GEPs in the patients with OGV was significantly lower than those without OGV.

In this study, GE in NI patients before surgery was strongly associated with OGV. Pre$T_{1/2}$ and preGEC in the patients with OGV were significantly longer compared with those in the patients without OGV. OGV results from the rotation of the stomach around the axis that bisects the lesser and greater curvatures of the stomach. These stomach positions may have a negative effect on the gastric middle, antral, and pyloric portions' motility. Since NI patients were in a nearly supine position, we speculate that stomach contents, such as liquid diets, stayed in the fundus. Indeed, Matsukubo et al. reported that patients with an elevated stomach position were at risk of developing DGE due to the abnormal position of their stomach [10].

Regarding the relation between GE and GER, Kawahara et al. reported that NI patients showed a wide range of GE rates without any significant causal relationship between DGE and GER [14]. In our study, there were no significant differences in GEPs between patients with GERD and those without GERD before surgery. In our previous study [5], significant moderately positive correlations were observed between both $T_{1/2}$ and T_{lag} and the non-acid reflux related parameters, which were not defined as pathological parameters of GERD in NI patients. However, a correlation analysis between ^{13}C-ABT parameters and the acid pH index and bolus exposure index revealed no statistical significance. We suspect that non-acid reflux may have occurred frequently because of the amount of the meal that pooled in the stomach due to DGE. We also suspect that other factors, such as the proximal gastric accommodation related to an increase in transient LES relaxation, which is known to be the main mechanism of GERD, may have affected the acid pH index.

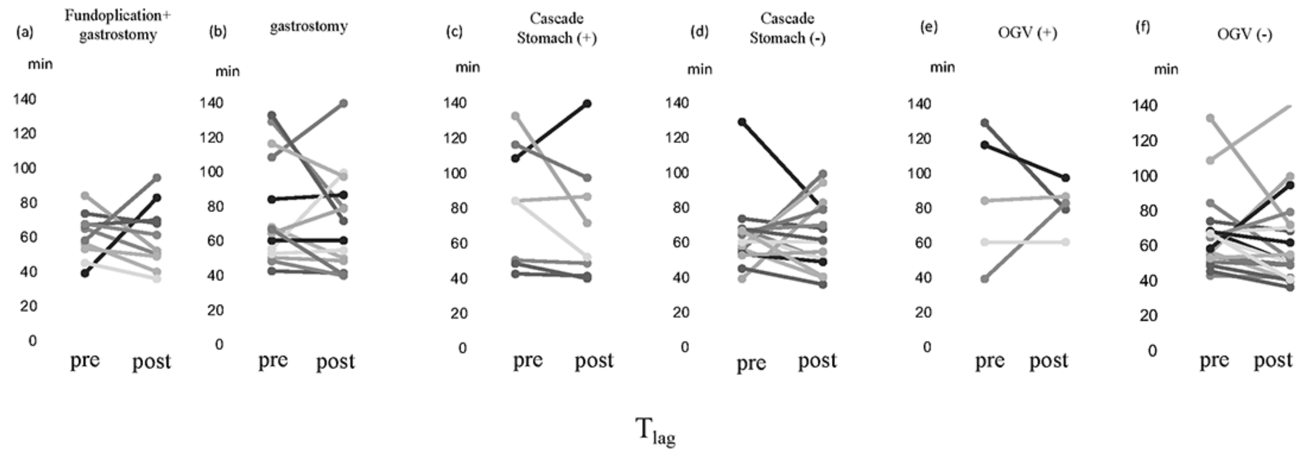

Fig. *2*. The comparison of T_{lag} between before and after surgery; (a) fundoplication + gastrostomy (b) gastrostomy, (c) with cascade stomach, (d) without cascade stomach, (e) with OGV, (f) without OGV.

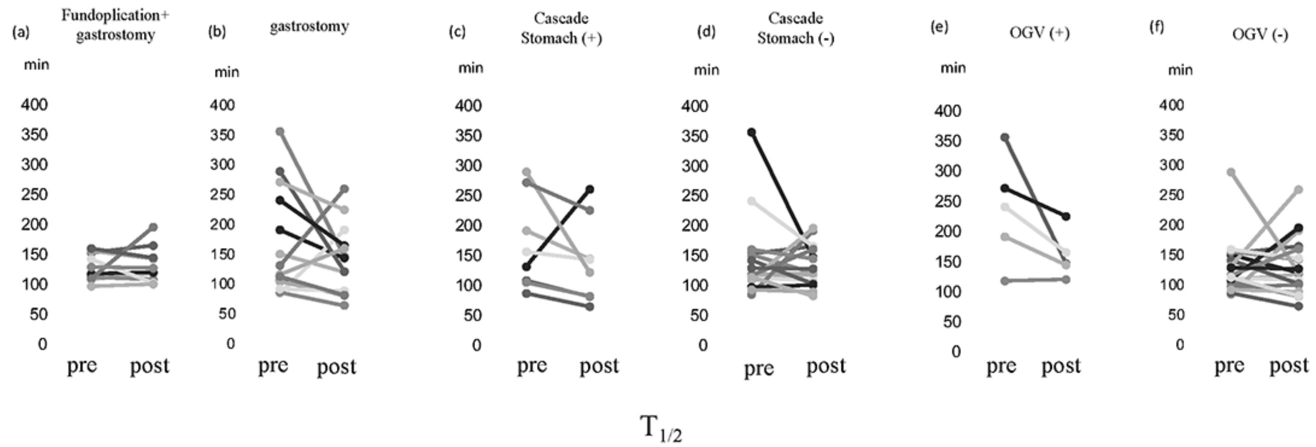

Fig. *3*. The comparison of $T_{1/2}$ between before and after surgery (a) fundoplication + gastrostomy (b) gastrostomy, (c) with cascade stomach, (d) without cascade stomach, (e) with OGV, (f) without OGV.

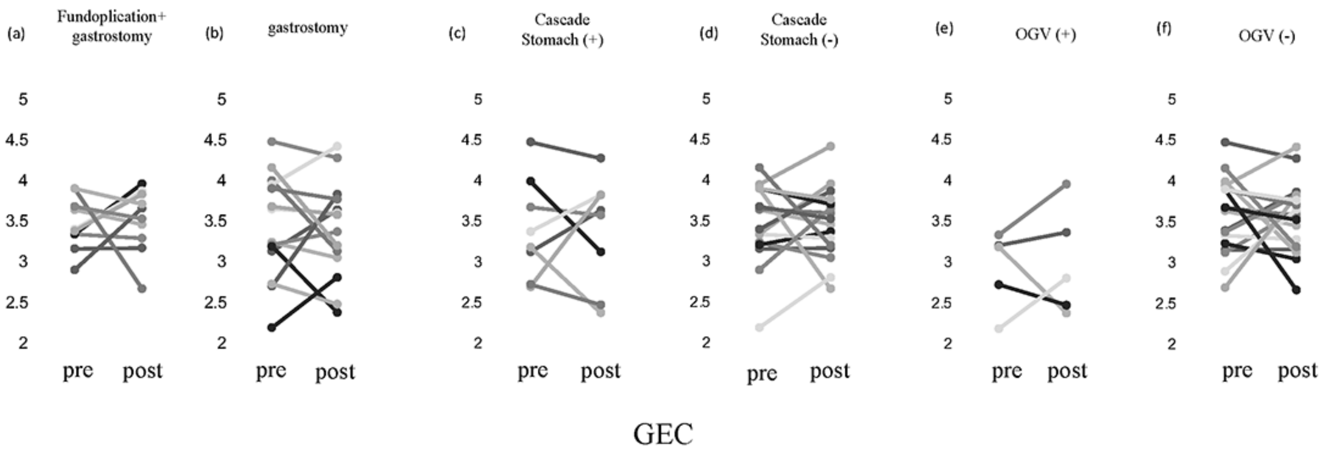

Fig. *4*. The comparison of GEC between before and after surgery (a) fundoplication + gastrostomy (b) gastrostomy, (c) with cascade stomach, (d) without cascade stomach, (e) with OGV, (f) without OGV.

TABLE 4.
The comparison of the change in the gastric emptying parameters between the patient with and without funduplication and morphology of the stomach (n=24)

	gastrostomy with funduplication (n=10)	gastrostomy (n=14)	*p*
ΔT_{lag} (min)	−5.95 (−15.2, 11.3)	−1.5 (−20.8, 5.47)	0.9068
$\Delta T_{1/2}$ (min)	0.37 (−13.7, 10.4)	−28.4 (−54.2, 8.28)	0.0601
ΔGEC	0.01 (−0.19, 0.55)	−0.12 (−0.18, 0.51)	0.5005
	cascade stomach (+) (n= 8)	cascade stomach (−) (n= 16)	*p*
ΔT_{lag} (min)	−5.14 (−28.7, 1.58)	−4.99 (−15.9, 11.5)	0.4440
$\Delta T_{1/2}$ (min)	−24.6 (−46.9, −15.4)	−2.59 (−31.0, 11.4)	0.1880
ΔGEC	−0.15 (−0.67, 0.50)	−0.05 (−0.19, 0.47)	0.6025
	OGV (+) (n=5)	OGV (−) (n=19)	*p*
ΔT_{lag} (min)	0 (−34.5, 23.1)	−5.61 (−16.2, 2.98)	0.9433
$\Delta T_{1/2}$ (min)	−47.1 (−142.7, −22.1)	−3.78 (−26.6, 12.0)	0.0291
ΔGEC	0.16 (−0.53, 0.51)	−0.1 (−0.19, 0.47)	0.7222

GEC=gastric emptying coefficient, OGV=organoaxial gastric volvulus. Data is expressed as median (25th, 75th interquartile range)

Two previous studies have investigated the effect of gastrostomy on GE in adults and detected no significant changes in GE after PEG with GE scintigraphy and electrogastrography [15,16]. In our study, GEPs in patients without GER were not significantly different before and after LAG. In children, there were two studies on LAG and GE using the ^{13}C-acetate or ^{13}C-octanoid acid breath test [6,13]. Franken et al. revealed that gastrostomy in children causes a significant delay in GE. Moreover, even patients with normal preoperative GE developed DGE after LAG [6]. They did not evaluate the relationship between GE and GER. Furthermore, their median patient age was 3.4 years old, compared with our median patient age of 13.5 years old. These discrepancies may explain the difference in GE after LAG between Franken's results and our own. Kawahara et al. also reported that the $T_{1/2}$ in patients without GER was not markedly different after LAG [13] as we did.

In our study, the GEPs of the patients who received the fundoplication and LAG did not have statistical significance between before and after surgery. Noble et al. reported that fundoplication reduced the fundic volume and impaired the stomach's ability to accommodate and store food, although this may have accelerated liquid and even solid GE [17]. On the other hand, since the increased LES pressure after fundoplication impaired belching and aggravated or produced symptoms of bloating and fullness, it might be associated with the development of DGE. Therefore, it will be difficult to investigate the effect of gastrostomy with fundoplication on GE in patients with GERD.

Regarding cascade stomach, there were no significant differences in GEPs before surgery or in the changes in GEPs between patients with cascade stomach and those without cascade stomach. As the NI patients were examined in the semi-Fowler's position, fixation of the stomach on the opposite side of the gastric angle did not change the morphology of the gastric fundus. This surgical procedure may not affect the gastric fundic lag phase on GE. We speculated that GEPs in cases of cascade stomach will not be associated with the type of surgery, e.g., LAG with or without fundoplication.

The change in $T_{1/2}$ ($\Delta T_{1/2}$) in the patients with OGV was -47.1 min, and that in the patients without OGV was -3.78 min, showing a significant difference. OGV was thus deemed to be the factor most strongly affecting GEPs that were dependent on surgery, including LAG as well as fundoplication in NI patients. Kawahara et al. reported that pulling down the stomach caudally below the costal arch during laparoscopic gastrostomy could correct the chronic OGV and possibly improved DGE [13]. In our study, the median $T_{1/2}$ in patients with OGV decreased from 241.3 mins to 147.1 mins after LAG with fundoplication or LAG only, without a significant difference (p=0.125). We speculated that the number of patients with OGV was small. The $T_{1/2}$ of 4 patients with OGV were improved for operation. However, the $T_{1/2}$ of the other patient with OGV was not changed for operation, because the pre$T_{1/2}$ of the patient was faster than pre$T_{1/2}$ of the other 4 patients with OGV (Fig.3). Therefore, we evaluated the changes in GEPs. For the patients with OGV, modification of the OGV and fixation of the stomach wall, such as LAG, would likely improve GE.

The present study was associated with several limitations. First, a relatively small number of patients with a wide age distribution, ranging from children to adults, were enrolled. Therefore, we did not take the age distribution into consideration. Second, the dosage of the test meal was calculated according to the body weight of each patient because, in comparison to neurologically normal subjects of the same age, it may be difficult to determine the optimal test meal dose for NI patients due to the presence of growth failure and wasting. However, several reports have determined the optimal dose based on body surface, while others use the recommended dose of 200 mL for adults [5,8]. Such limitations in the present study may have affected the results. Third, according to the surgical procedure, despite the difference in surgical procedures between patients with GERD who underwent Nissen's fundoplication and LAG and those without GERD who underwent LAG only, the breath endpoints in this study did not show statistically significant differences. There may have been some bias between patients who underwent fundoplication + LAG versus LAG only. Future prospective studies that provide more accurate results and are less influenced by bias are warranted.

CONCLUSION

In conclusion, GE in NI patients with OGV was significantly longer compared with those without OGV before surgery. Modification of stomach malposition and fixation of the stomach wall may be able to help improveme GE in NI patients with OGV. Further studies in larger cohorts are required to elucidate the mechanism of improvement in DGE.

CONFLICTS OF INTEREST: None.

ACKNOWLEDGMENTS/FINANCIAL SUPPORT: None.

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